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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
SUITE 3200
CHICAGO, IL 60606

EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,256	DUNLAY ET AL.	
	Examin r	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/12/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,44-50,54,55 and 57-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,44-50,54,55 and 57-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendments and remarks in Paper No. 12, filed 3/12/03, are acknowledged. Cancellation of claims 51-53 and 56 and amendment of claims 30, 44-50, 54-55, 57-60, 62, and 64 are acknowledged.

Applicants' arguments, filed 3/12/03, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to a system for cell-based screening whereas in contrast the elected claims include a machine readable storage medium containing instructions for a cell screening system to detect macromolecule distribution between cellular compartments.

Applicants note on page 10 of their Response, filed 3/12/03, that the Office Action Summary sheet (PTO-326 form) states that claims 30 and 44-65 are subjected to a restriction and/or election requirement and that the Office Action did not specifically state a restriction requirement. As claims 1-29 and 31-43 were cancelled in a preliminary amendment filed 11/27/00, no restriction requirement was ever set forth. The checked box number 8 on PTO-326 form was an inadvertent error and this non-existent restriction requirement is hereby withdrawn.

Claims 30, 44-50, 54-55, and 57-65 are herein under examination.

Terminal Disclaimer

The terminal disclaimer, filed 3/12/03, has been approved which therefore nullifies the provisional obviousness-type double patenting rejection as stated in the previous two Office actions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30, 44-50, 54-55, and 57-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30, 45-50, 54-55, 57-60, and 64 (Applicants' response page 2, lines 5 and 21; page 3, lines 2, 12, 17, 22, 23, 27, and 31; page 4, lines 3, 10, 13, 15, 18, 22, and 25; page 5, lines 5, 8, and 12; page 6, lines 5, 10, 16, 19, 21, and 24; page 7, lines 4, 10, and 23; and page 8, line 1) describe the detection of macromolecule(s) of interest "on and/or in" individual or multiple cells to detect the distribution between a nucleus and cytoplasm. As written, the two options for detection include detection *on* cells or detection *in* cells. It is unclear how the distribution between a nucleus and cytoplasm is detected "on" individual cells when the nucleus and cytoplasm are presumably "in" said cells. Claims 44, 61-63, and 65 are also rejected due to their direct or indirect dependency from claim 30.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

The Applicants maintain that the Akong et al. in view of Lee et al. do not teach or suggest all of the claim limitations. Further explanation of the prior art rejections is described below.

Claims 30, 44-50, 54-55, and 57-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akong et al. (P/N 5,670,113), in view of Lee et al. (P/N 5,627,908), St. George-Hyslop et al. (P/N 6,020,143), Salpeter et al. (Journal of Cell Biology, 1981,Volume 91, pages 240-246), and *In re Venner*.

Akong et al. teach an automated measurement apparatus and computer-controlled methods to screen cells to which a fluorescent reagent has been added and identify sample

attributes associated with these cells (abstract and col. 1, lines 11-18 and 40-43). Akong et al. teach plate readers which read (scan) an array of wells (col. 1, lines 40-43), including their invention that can measure at least one attribute (col. 2, lines 65-66) by emitted light (col. 3, lines 36-46). The biological samples that can be identified include proteins such as enzymes (col. 1, lines 18-20) and cell surface ion channels and receptors (col. 2, lines 10-14) which fall under the categories of fluorescent reporter molecules in the instant invention. The mask as described in the instant specification is a binary image with the objects displayed in white and the background displayed in black (page 32, lines 19-21). Akong et al. teach the background fluorescent levels may occur in the sample before the reagent is added which warrants the measurement of background (pre-reagent) values (intensity) to be incorporated in the post-reagent analysis (col. 3, lines 47-56), effectively creating a mask. Akong et al. teach taking multiple fluorescent measurements before, during and after the reagent is pumped into the wells (col. 4, lines 16-21) as a variety of agents may be added to the wells once or in multiple times (col. 4, lines 37-40). Akong et al. teach the method of testing the cellular response to the added reagents (col. 4, lines 64-67) and measuring the changes in fluorescent intensity to detect a change in the concentration of molecules (col. 5, lines 1-9). Akong et al. teach that this assay can include control samples (col. 5, line 37), as well as single or sequential additions of reagents (col. 5, lines 39-41). Akong et al. teach that this assay may include living cells (col. 5, line 18). Akong et al. teach this assay encompasses the detection differences in fluorescence intensities in a solution as a consequence of a cellular event which allows the assay to be used on any compound capable of differential fluorescence to change in response to a cellular event (col. 27, lines 15-34). Akong et al. teach the use of various fluorescent indicator (reporter) molecules, such as calcium-sensitive, chloride-

sensitive, sodium-sensitive, and potassium-sensitive fluorescent indicators for these assays (col. 17, lines 25-40, col. 22, lines 18-41, and Table on cols. 21 and 22). Akong et al. do not describe fluorescent reporter molecules, including labeled antibodies, that report on two or more cellular compartments such as a cell membrane, endoplasmic reticulum, or Golgi apparatus as well as their masks. Akong et al. do not describe nuclear and cytoplasmic masks. Akong et al. also do not describe a machine readable medium.

Although Akong et al. teach this method above on a computer-driven apparatus, they do not teach having this program on a machine readable storage medium using computer-executable instructions. *In re Venner* 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) states that it is obvious to computerize a manual activity. The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over prior art as stated in MPEP § 2144.04, Part III.

Lee et al. disclose the use of a computer to identify multiple cell patterns (col. 5, lines 24-25) via an image analysis system (col. 14, lines 54-55) on fixed cells on a slide (col. 5, lines 34-39). While providing over 15,000 fields of view for one specimen, not all fields are of interest (col. 14, lines 58-60). A mask is provided to express a unique identification value including size, shape and location for the object of interest (col. 15, lines 15-18) for both the nucleus and cytoplasm of each cell (col. 15, lines 29-30). Lee et al. teach that the brightness of the object within the predetermined range (nucleus, cytoplasm, or background) is determined (col. 15, lines 42-46 and col. 16, lines 3-4). Lee et al. disclose the background can be normalized to aid in detecting images where the objects of interest include two portions having different levels of brightness (intensity) such as the nucleus and cytoplasm (col. 17, lines 53-66). Lee et al. disclose

the act of eroding the objects of a mask (such as the nuclear mask) and then dilating them by a second predetermined amount where the amount of erosion exceeds the amount of dilation to separate connected objects and create another mask (cytoplasmic mask, in this case) (col. 20, lines 34-54).

St. George-Hyslop et al. describe screening compounds within cells based on their effects on trafficking and localizing proteins in the endoplasmic reticulum and Golgi apparatus (col. 64, lines 30-36). Detection techniques of this localization employ fluorescently or radioactively labeled antibodies to visualize this intracellular localization (col. 64, lines 43-52).

Salpeter et al. describe using a masking procedure to compare distributions to identify labeled sources in the tissue (abstract, lines 4-9). Salpeter et al. describe obtaining intracellular and intercellular data on labeled structures (page 242, col. 1, lines 1-2). A computer program compares two distributions to identify the labeled sources in tissue (abstract, lines 6-9). Intracellular transport of proteins from the endoplasmic reticulum to the Golgi complex was studied with precision labeling of the individual source compartments (abstract, lines 10-15). Salpeter et al. describe comparing labeled compartments, such as ER, with cytoplasm labeled areas (abstract, lines 17-23). Salpeter et al. describe using several compartments such as endoplasmic reticulum, Golgi apparatus, cytoplasm as well as background between cells and other cells (page 242, col. 1, lines 5-13). As Salpeter describe the ability to detect label concentration even from very small structures which constitute a small percentage of the total cell area (abstract, lines 25-28), it would appear obvious for this to include a compartment such as a cell membrane. Salpeter et al. describe the masks are used to determine distribution of labeled grains via grain density analysis from assumed sources (abstract, lines 4-9). Salpeter et

al. describe using the "mask" analysis method, including tabulating the distribution of data points and using masks to generate expected distributions (page 241, col. 2, lines 20-25). A computer program was utilized to compare the distributions and vary the relative intensity until a best fit was found between expected and observed distributions (page 241, col. 2, lines 26-28).

A skilled artisan in the art would have been motivated to enhance the procedures of detecting distribution of cellular macromolecules, as stated by Akong et al., by including these steps on a computer readable medium in order to easily and efficiently gain an understanding of the roles of compounds in drug screening assays, as stated by Akong et al. (abstract). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to place computer-executable instructions on a machine readable storage medium for a manual activity (as discussed by *In re Venner*) such as the basic identification of macromolecular distribution in cells (as stated by Akong et al.), because this information would enhance and quicken access to the identification of compounds to be used as drugs, as stated by Akong et al. (abstract).

Akong et al. state the need for rapidly screening compounds to determine the effects and concentrations of molecules within a cell during drug screening in order to identify potential pharmaceuticals (col. 2, lines 10-14 and col. 5, lines 10-19). Akong et al. use computer-controlled methods to assay the activity and distribution of molecules within cells, particularly the cytoplasm of a cell (col. 2, lines 56-67; col. 3, lines 1-2; and col. 5, lines 4-9). A skilled artisan would have been motivated to enhance the machine readable storage medium with a method of identifying the distribution of molecules via fluorescent indicator molecules, as stated by *In re Venner* and Akong et al., by including further steps of dividing the cell area under

examination in order to normalize variations and gain an accurate and rapid view of a particular area of interest, as stated by Lee et al. (col. 1, lines 7-8 and col. 15, lines 10-13). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to further compartmentalize the areas undergoing optical cell screening analyses (as stated by Akong et al.) via fluorescently labeled antibodies (as stated by St. George-Hyslop et al.) to make use of various cellular masks (as stated by Lee et al. and Salpeter et al.), because this would enhance the understanding and create a more accurate view of compounds that affect cells under study, as stated by Akong et al. (abstract).

Thus, Akong et al., in view of Lee et al., George-Hyslop et al., Salpeter et al., and *In re Venner*, motivate claims 30, 44-50, 54-55, and 57-65.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

May 22, 2003

ARDIN H. MARSCHEL
PRIMARY EXAMINER

ARDIN H. MARSCHEL
PRIMARY EXAMINER